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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/651,668	08/28/2003	Alexei Brooun	SYR-ISPA-5001-C1	9129

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TAKEDA SAN DIEGO, INC.
10410 SCIENCE CENTER DRIVE
SAN DIEGO, CA 92121

EXAMINER	
KIM, ALEXANDER D	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
10/02/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/651,668	BROOUN ET AL.	
	Examiner	Art Unit	
	ALEXANDER D. KIM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 4, 6, 9, 18, 19 and 21-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *19 and 24* is/are allowed.

6)☒ Claim(s) *1, 4, 6, 9, 18 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final rejection (mailed on 02/13/2008), Applicants filed a response and amendment received on 05/13/2008. Said amendment cancelled Claims 2-3, 5, 7-8, 10-17 and 20; and amended Claims 1 and 6.

Claims 1, 4, 6, 9, 18, 19 and 21-24 are pending in the instant Office action and will be examined herein.

Compliance with Sequence Rules

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to fully comply with the requirements of 37 C.F.R. 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

The polypeptide "DDXXD" on page 31, lines 7 and 8, is recited without SEQ ID NO. Appropriate correction is required.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the

content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 4, 6, 9, 18 and 21-23 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to previous Claims 1, 4, 6, 9-10, 18 and 20-23. In response to this rejection, applicants have amended Claims 1 and 6; and traverse the rejection as it applies to the newly amended claims. Applicants' argument has been fully considered but is not deemed persuasive for the following reasons.

Applicants traverse the instant rejection (in view of the instant amendment) on the basis that the written description requirement is satisfied when "the description

clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed" and "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter" (see bottom of page 4 to top of page 5). Applicants argue the claimed subject matter does not need to be described literally in order to satisfy the description requirement. Applicants argue that instant claims meet the written description requirement because the exact protein sequence and space group and unit cell parameters and the bisphosphonate or isoprenoid ligand are reasonable for written description requirement.

The Examiner acknowledges and agrees with the applicants' argument above as long as the claimed subject matter is in possession by one skilled in the art in view of the instant disclosure, or the instant disclosure teach a sufficient structure and functional correlation for the full scope of claimed subject matters which may not have literal description.

However, the scope of a bisphosphonate and an isoprenoid are narrower compared to previously recited "a ligand"; but said bisphosphonate and said isoprenoid still encompass genus molecules having very widely varying structure. Thus, the breadth of amended Claim 1 (Claim 4 dependent therefrom) is drawn to a very widely varying composition comprising a protein crystal, wherein the protein crystal is a co-crystal bound to any bisphosphonate or any isoprenoid ligand, wherein the crystal is consist of 1-314 of SEQ ID NO: 1 and the crystal has a crystal lattice in a $P4_122$ and the unit cell dimensions a=88.80 Å, b=88.80 Å, c=174.99 Å and $\alpha=\beta=\gamma=90^{o}$. As previously noted, the instant amended limitation of "said protein forms a complex with a

bisphosphonate or a isoprenoid ligand" in Claims 1 and 6 can be interpreted as binding capability of said protein as well as the co-crystal (or a method of making a co-crystal). Thus, one skilled in the art would not be able to possess the full scope of claimed invention by the virtue of instant disclosure lacking the disclosure of correlation between structure of composition and function of forming a protein crystal. The breadth of claim 6 (Claims 9, 18 and 21-23 dependent therefrom) is drawn to a very widely varying method for forming a crystal of a protein which is consist of 1-314 of SEQ ID NO: 1, in any suitable conditions encompassing unlimited mother liquor composition and their concentration as well as having unlimited molecule(s), compound(s) encompassed by the genus of any bisphosphonate or isoprenoid ligand. Thus, one skilled in the art would not be able to possess the full scope of claimed method by the virtue of instant disclosure lacking the disclosure of correlation between structure (i.e., a precipitant and a protein solution) and function (i.e., conditions suitable for forming a protein crystal when the suitable condition results in a protein crystal bound to any bisphosphonate or isoprenoid ligand). The fact that there are many publication or disclosure of protein crystallization in general has very minimal (almost none) support for providing the representative species for the instant claims because every crystallization is case by case basis, specially those publication or disclosure is not about the crystallization of a protein consisting of residues 1-314 of SEQ ID NO: 1. For the reasons above and the previous written description rejection, the instant rejection is maintained.

4. Claims 1, 4, 6, 9, 18 and 21-23 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for a crystal or a method for preparing a co-crystal of a polypeptide consisting of residues 1-314 SEQ ID NO: 1 by a method of crystallizing a ternary complex consisting of said polypeptide with ligands (IPP+Risedronate, see specification page 49), that results in a crystal having the space group $P4_122$ and the unit cell dimensions a=88.80 Å, b=88.80 Å, c=174.99 Å and $\alpha=\beta=\gamma=90^{o}$; does not reasonably provide enablement for all crystals and methods comprising the steps of using any suitable condition for the preparation of the co-crystal as broadly encompassed by the breadth claims that is any crystal of 1-314 of SEQ ID NO: 1 (or method of forming said crystal thereof) complex with in the presence of any bisphosphonate or any isoprenoid ligand.

The rejection was stated in the previous office action as it applied to previous Claims 1, 4, 6, 9-10, 18 and 20-23. In response to this rejection, applicants have cancelled Claims 2-3, 5, 7-8,10-17 and 20; amended Claims 1, 6 and 23 and traverse the rejection as it applies to the newly amended claims. Applicants' argument has been fully considered but is not deemed persuasive for the following reasons.

Applicants traverse the instant rejection because the standard for determining whether the specification meets the enablement requirement is by a determination whether any undue experimentation is necessary. Applicants argue the claimed subject matter does not need to be described literally in order to satisfy the description requirement. Applicants argue that instant claims are enabled without undue experimentation because the exact protein sequence and space group and unit cell

parameters and the bisphosphonate or isoprenoid ligand and the variability of instant disclosure is simple for one skilled in the art to screen a protein crystal encompassed in the claims.

However, the scope of a bisphosphonate and an isoprenoid are narrower compared to previously recited "a ligand"; but said bisphosphonate and said isoprenoid still encompass genus molecules having very widely varying structure. As noted previously, the instant amended limitation of "said protein forms a complex with a bisphosphonate or an isoprenoid ligand" in Claims 1 and 6 can be interpreted as binding capability of said protein as well as the co-crystal (or a method of making a co-crystal). The undue experimentation is necessary for one skilled in the art to make and use the full scope of claimed subject matter for the following reasons. The breadth of amended Claim 1 (Claim 4 dependent therefrom) is drawn to a very widely varying composition comprising a protein crystal, wherein the protein crystal is a co-crystal bound to any bisphosphonate or any isoprenoid ligand, wherein the crystal is consist of 1-314 of SEQ ID NO: 1 and the crystal has a crystal lattice in a $P4_122$ and the unit cell dimensions a=88.80 Å, b=88.80 Å, c=174.99 Å and $\alpha=\beta=\gamma=90^{o}$. The breadth of claim 6 (Claims 9, 18 and 21-23 dependent therefrom) is drawn to a very widely varying method for forming a crystal of a protein which is consist of 1-314 of SEQ ID NO: 1, in any suitable conditions encompassing unlimited mother liquor composition and their concentration as well as having unlimited molecule(s), compound(s) encompassed by the genus of any bisphosphonate or isoprenoid ligand.

Examiner acknowledges that a routine experiment, which is simple to change variability, does not automatically require an undue experimentation. It is true that one skilled in the art can screen very widely varying crystallization condition which is simple to just make and mix any precipitant using commercially available kit and robotic operation without undue experimentation. However, to make and use such screening method to be a conditions suitable for formation of a protein crystal of residues 1-314 of SEQ ID NO: 1 in the presence of any bisphosphonate or any isoprenoid form the co-crystal, would require a undue experimentation in view of very broad claimed crystal and/or claimed method of crystallization and unpredictability of forming a genus of claimed protein co-crystal (or method of forming thereof). The simple procedure to making and mixing any precipitant in the presence of any bisphosphonate or any isoprenoid does not decrease the unpredictability nature of protein crystallization. Thus, instant claims are very unpredictable to make and use the claimed protein crystal (or method of crystallization thereof). This is the reason one skilled in the art first attempt to screen as broad crystallization conditions as possible, which is also supported by Applicants' own disclosure reciting the wide range of crystallization conditions disclosed by the present invention provide guidance to further explore for new conditions to grow the claimed crystal" (see bottom of page 8, Remark filed on 08/06/2007). The said further exploration is what makes one skilled in the art to require an undue experimentation for protein crystallization in the presence of any bisphosphonate or any isoprenoid, especially when the claims are drawn to a very widely varying genus as described above in the breadth of claims. Thus, the instant disclosure and the prior art

failed to provide the guidance or direction to make and use the full scope of claimed invention without undue experimentation for one skilled in the art. For the reasons above and the previous office action, the instant rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

5. Claims 1, 4, 6, 9, 18 and 21-23 are rejected under 35 U.S.C. 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 (Claim 4 dependent therefrom) is drawn to a composition comprising a protein in crystalline form, wherein the protein consists of residues 1-314 of SEQ ID NO: 1. Claim 1 is amended by adding new limitation "bisphosphonate or isoprenoid"; thus, claimed product encompasses a composition comprising a protein in crystalline form and said protein in a crystalline forms is in a complex with a bisphosphonate or isoprenoid ligand, wherein the crystal has a crystal lattice in a $P4_122$ space group and the unit cell dimensions, +/- 5%, of a=88.80 Å, b=88.80 Å, c=174.99 Å and $\alpha=\beta=\gamma=90^{\circ}$.

The applicant is advised to point out the support in the original disclosure or amend the instant claims. Applicants disclose that the amendment of Claim 1 is supported by the paragraphs [0117] and [0183]. However, the paragraph 0117 only discloses that the IspA structure has cavity that binds the isoprenoid substrate as well as bisphosphonate inhibitor.

The paragraph 0183 only disclose the protein (1-314 of SEQ ID NO: 1) in crystalline form with ligand, wherein ligand is directed to a specific compounds (i.e., isopentyl pyrophosphate (IPP) + dimethylallyl S-thiolodiphosphate (DMASPP); IPP + farnesyl S- thiolodiphosphate (FSPP); geranyl diphosphate (GPP); IPP + geranyl S-thiolodiphosphate; IPP + Risedronate; IPP + Pamidronate, or Risedronate).

The limitation of Claim 1 reciting "said protein forms a complex with a bisphosphonate or isoprenoid ligand", as shown with underline above, is not supported by the original disclosure and is thus considered new matter.

6. Claim 6 (Claims 9, 18 and 21-23 dependent therefrom) is rejected under 35 U.S.C. 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 6 (Claims 9, 18 and 21-23 dependent therefrom) is drawn to a method for forming a crystal of a protein comprising a protein comprising: forming a crystallization

volume comprising a precipitant solution and a protein that consists of residues 1-314 of SEQ ID NO: 1, wherein said method encompasses forming a crystallization volume comprising the protein in crystalline form is complexed with a bisphosphonate or isoprenoid ligand; and storing the crystallization volume under conditions suitable for formation of a protein crystal~ wherein the protein crystal has a crystal lattice in a $P4_122$ space group and unit ceil dimensions, +/- 5%, of a=88.80 Å, b=88.80 Å, c=174.99 Å and $\alpha=\beta=\gamma=90^{o}$.

The applicant is advised to point out the support in the original disclosure or amend the instant claims. Applicants disclose that the amendment of Claims 6 is supported by the paragraphs [0117] and [0183]. However, the paragraph 0117 only discloses that the IspA structure has cavity that binds the isoprenoid substrate as well as bisphosphonate inhibitor.

The paragraph 0183 only disclose the protein (1-314 of SEQ ID NO: 1) in crystalline form with ligand, wherein ligand is directed to a specific compounds (i.e., isopentyl pyrophosphate (IPP) + dimethylallyl S-thiolodiphosphate (DMASPP); IPP + farnesyl S- thiolodiphosphate (FSPP); geranyl diphosphate (GPP); IPP + geranyl S-thiolodiphosphate; IPP + Risedronate; IPP + Pamidronate, or Risedronate).

The limitation of Claim 6 reciting "said protein forms a complex with a bisphosphonate or isoprenoid ligand", as shown with underline above, is not supported by the original disclosure and is thus considered new matter.

Conclusion

7. Claims 19 and 24 are allowable. Claims 1, 4, 6, 9, 18 and 21-23 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered section in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander D. Kim whose telephone number is (571) 272-5266. The examiner can normally be reached on 11AM-7:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Bragdon can be reached on (571) 272-0931. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alexander D Kim/
Examiner, Art Unit 1656

/Richard G Hutson, Ph.D./
Primary Examiner, Art Unit 1652